The dexamethasone suppression test as a variable in clinical diagnosis and research

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The dexamethasone suppression test as a variable in clinical diagnosis and research: a review

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Introduction

In 1981 Carroll *et al.*[1] introduced the dexamethasone suppression test (DST) as a routine aid in the diagnosis of melancholia. Some years have since passed and it seems useful to consider the following questions:

(*a*) Is the DST a biological marker in psychiatric diagnosis?

(*b*) Does the DST have a specific function as an aid in the diagnosis of certain types of depression?

(*c*) What is the significance of the DST as an independent variable?

Definitions of biological markers will be given and their range of applications outlined before the above questions are discussed in detail and some considerations offered. In this context the term 'vital'[2] is equated to 'endogenous', 'primary', 'major' and 'melancholic'. This is done in part because the DST sensitivity of vital depressions can be expected to be similar to that of depressions designated by the other adjectives mentioned[3].

Biological markers

These are indicators with the aid of which behaviour may be understood or explained. A 'trait marker' may be permanently present regardless of the nature, severity and course of the disease behaviour. A 'state marker' is dependent on the phase of the disease process and may appear in the initial phase, in the course of or after the illness. Roughly, four groups of markers can be distinguished.

(1) Causal markers: These indicators relate to the pathophysiological aspects of the disease process. The postulate is that the causal (aetiological and pathogenetic) factors of the disease are more readily traceable as the diagnostic significance of the marker increases. With the inaccessibility of brain tissue, psychiatric and neurobiological investigations must of course concentrate on peripheral parameters such as cerebrospinal fluid (CSF), blood and urine.

(2) Metabolites of the disease process: The test substance serving as marker is usually not the cause but rather the (end-)product of the physical process. An excess of noradrenaline (NA), for example, may be the cause of disturbances in synaptic processes. The NA metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) – an indicator of (increased) NA production – is not harmful *per se*. In some cases it is not (yet) possible to establish whether the marker is cause or consequence of the illness. An example may be found in the enlarged ventricles (due to cerebral atrophy) of chronic schizophrenic patients. In principle this marker is bifunctional: it may be cause or effect of a schizophreniform psychosis.

(3) Test markers: A metabolic disorder such as diabetes often cannot be diagnosed until after provocation with a high-sugar diet (glucose tolerance test). Parallel to this, psychiatry uses psychotropic substances and hormones for further investigation of certain neurotransmitter and/or endocrine systems. The DST could be an example of this.

(4) Genetic markers: These have no functional relation to metabolic processes but derive their significance from their presence on the pathogenic chromosome. Not only are such markers – e.g. that of colour blindness – found more often in relatives of depressive patients, they are also represented in other family members who are likewise ill. It may thus be postulated that colour blindness – as a manifestation of a central nervous system (CNS) dysfunction – and the X-chromosome responsible for this phenomenon, can contribute to the development of another CNS disorder, e.g. depressive behaviour.

The DST as biological marker

Over 400 publications[4] have so far reported on the use of the DST as an aid in psychiatry. It may be used, for example, as an aid in the diagnosis of disorders of adrenal function, as in Cushing's syndrome. Carroll *et al.*[1] found diminished suppression or non-suppression in over 50% of the vital depressive patients studied; in other words, in these patients the plasma cortisol concentration returned to normal more quickly than it did in a control group. This demonstrates that, in principle, the function of the hypothalamo-hypophyseo-adrenal axis is disturbed in depressive patients. Non-suppression is more likely to occur after a dose of 1 mg dexamethasone[5] (at 11 pm the previous day) than after ingestion of 1.5 mg[6] or 2 mg[1]. More than 50% of the non-suppression results were obtained in the afternoon (4 pm); some 20% were obtained about 24 hours after dexamethasone ingestion (at 11 pm). These studies have led to widespread acceptance of the DST as a biological marker in psychiatry[3].

The DST in the diagnosis of depressive behaviour

How specific is the DST for depression?

The suggestion that the DST might be a fairly specific aid in the diagnosis of depression has not

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been confirmed. Dexamethasone non-suppression has been observed in many other psychiatric disorders[3]: alcoholism, obsessive-compulsive behaviour, atypical psychoses, schizophreniform disorders, schizo-affective psychosis[7], schizophrenia, manic agitation, dementia, borderline personality, anorexia nervosa[8] and bulimia. It would not be surprising if this list proved to be even longer.

Conceivably, the DST might be so (in)sensitive as an indicator of a hypothalamo-hypophyseo-adrenal axis disorder that its specificity for depression (i.e. the percentage of suppression in non-depressive persons) would be of little clinical relevance. Berger *et al.*[6] made more or less the same observation, although they described it as lack of specificity of the DST for depression. The postulate that DST non-suppression in the case of disturbed behaviour is an expression of a hypothalamo-hypophyseo-adrenal axis disorder on a cerebral level, seems plausible. The importance of pharmacokinetic factors[9,10], such as reduced bioavailability of dexamethasone in the case of DST non-suppression, seems quite obvious. Moreover, DST non-suppression is at least partly due to increased serum cortisol concentrations and/or increased dexamethasone degradation[11].

How specific is the DST for vital depression?

Carroll *et al.*[1] stressed that a disturbed DST may be expected in some 50% of persons suspected of suffering from a vital depression (according to their laboratory criteria, DST non-suppression exists at a serum cortisol level $>5\ \mu g/dl$). However convincing this conclusion may seem, in practice DST non-suppression may be encountered both in non-vital depressions and in normal test subjects[3]. This suggests that the so-called sensitivity of the DST (i.e. the percentage of non-suppression in vital depressive patients) is much lower than is desirable. Insel and Goodwin[12] studied seven reports on DST sensitivity assessment and concluded that the mean sensitivity does not exceed 40%. The DST has been described as a test of limited significance in the differential diagnosis of vital depressions[13].

Our conclusion is that the DST in its present form and mode of application has some (but as such insufficient) significance if used alone (not combined with other markers) as an aid in the diagnosis of vital depressive syndromes.

What is the DST's predictive role?

The role of the DST as a predictor of the course of depressions and their response to therapy is rather uncertain. Greden *et al.*[14] unsuccessfully attempted to find significant differences between pre- and post-therapeutic hypothalamo-hypophyseo-adrenal axis variables (such as serum cortisol concentration following dexamethasone administration) in depressive patients responding well to imipramine and amitriptyline respectively. Non-suppression in the DST can, however, predict a favourable response to electroconvulsive therapy (ECT) if the test is done upon discharge from hospital instead of six months later[15]. Greden *et al.*[16] performed the DST weekly and observed normalization in most non-suppressors if they showed a good clinical response to antidepressants. Targum[17] reported a similar trend: the DST predicts whether vital depressives will improve in response to antidepressants. However, in the case of recurrence of non-suppression after normalization of the test – even when patients improve in response to antidepressant medication – there is a grave risk of clinical relapse[14].

Peselow *et al.*[18] were unable to confirm whether the DST can predict specificity of antidepressant medication. On the whole, however, the DST may be an objective aid in research concerning the prediction of and tolerance to antidepressant medication[13]. The fact that a DST is disturbed in vital depression does not as such provide sufficient certainty about the clinical course, nor an indication of the antidepressant of choice[9].

The DST as independent variable

The DST may also be studied in relation to separate symptoms, e.g. weight loss and stress. Weight loss is related to non-suppression in the DST in both depressive and non-depressive patients[3,9]. Ceulemans *et al.*[19] found DST non-suppression in the case of preoperative stress. Zimmerman and Ostrow[20] found no indication that the Hamilton Depression Rating Scale (HDRS) could clinically differentiate DST suppressors and non-suppressors. What is of interest is the relationship between psychopathological variables (suicidal tendency, anhedonia, mood, etc.) and the DST[21].

It seems evident that rating scales are important in treating persons with dysfunction of the hypothalamo-hypophyseo-adrenal axis[22]. Mellsop *et al.*[23] have postulated that the degree of non-suppression in the DST might correspond with the degree of stress or distress of the person tested. It seems possible that quite apart from its currently still modest importance in the biological field, the DST could become increasingly important in psychosocial research in the years to come[24]. In behaviour research, tests may assist pharmacologists, psychologists as well as medical investigators in gaining a better understanding of human functioning as a biopsychosocial phenomenon.

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